

ROLE OF MYOSTATIN PATHWAY IN MUSCLE GROWTH: KEY LEARNINGS FROM RETROSPECTIVE ANALYSIS OF MYO-029 PRECLINICAL AND CLINICAL DATA THRU PK/PD MODELING

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Abstract

BACKGROUND: Suppression of Myostatin (i.e. GDF-8) pathway is considered an important therapeutic strategy for the treatment of muscle-wasting disorders, including muscular dystrophy, cachexia and sarcopenia. Myostatin is a member of TGF- β superfamily and negatively regulates skeletal muscle mass, muscle fiber size and fiber count. Clinical trials targeting the Myostatin pathways have produced mixed results - ACE-031, an Fc fusion of ActRIIB decoy receptor of GDF-8 was reported to increase muscle mass in Phase I/II trials with healthy post-menopausal women and Duchenne muscular dystrophy (DMD) patients. In contrast, MYO-029, an antibody against Myostatin failed to achieve clinical efficacy in DMD patients. Given these contrasting results, it is critical to understand whether the clinical and preclinical data support GDF-8 as a novel paradigm for the treatment of muscular dystrophy disease.

METHODS: We performed a detailed pharmacokinetic-pharmacodynamic (PK/PD) analysis of preclinical and clinical data on MYO-029 to address animal model translation and predict the level of target inhibition at the clinical doses. A combination of mouse, non-human primates, and clinical data were analyzed and exposure-response relationships were established for various pharmacodynamic endpoints. These include muscle weight increase in SCID mice efficacy studies, muscle circumference changes in 39-week toxicology study in monkeys, and total myostatin levels observed in multiple-ascending dose (MAD) studies in Phase I/II trials.

RESULTS: Our modeling analysis revealed a significant in-vivo potency shift between mice and monkeys species. Further, our results show that the exposures of Myo-029 in humans had low probability of success in modulating the target to result in robust efficacy.

CONCLUSION: The PK/PD analysis presented in this report support the rationale for therapeutic strategies targeting myostatin pathway.